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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,976	12/05/2005	Seetharama A. Acharya	96700/1023	6788

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,976	ACHARYA ET AL.	
	Examiner	Art Unit	
	SAMUEL W. LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-21* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 8-21 are pending.

The amendment filed 5/7/08, which amends claim 8 and cancels claim 28, has been entered. Claims 8-21 are examined in this office action.

Withdrawal of the Objection

The objection to claim 28 is withdrawn in light of the cancellation of said claim.

Objection to claims

The claims are objected to because of the following informalities:

Claims 8-21 are objected to in the recitation of "fold excess". Based on the specification and applicant's arguments, it is clear that the term "fold excess" is intended as being interpreted as "fold molar excess" and in order to substantially improve claim form, it is suggested that the noted phrase be amended to recite "fold molar excess".

New-Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Acharya et al. (US Pat. No. 6017943) in view of Nho et al. (US Pat. No. 5,234,903).

CLAIM INTERPRETATION: Claim 8 recites the phrase "modified to have six ± one polyethylene glycol…", wherein the transitional phrase "have" has been broadly, but reasonably interpreted as being open-ended. Thus, the claims have been interpreted as a process for preparing a Hb with *at least* – but not limited to – six ± one PEGs.

At col. 7, line 64 to col. 8, line 26, Acharya et al. teach preparation of polyethylene glycol (PEG) modified hemoglobin (Hb) which comprises the steps: (i) reacting Hb with a thiolating agent, e.g., iminothiolane, and (ii) reacting with the thiolated "Hb" with the "PEG compound" which is produced by conjugation with a compound containing maleimide moiety, e.g., 4-(or 3-)-phenylmalemimido (col. 8, line 4 and Examples 5-6). At the same column, lines 22-27, and patent claim 4, Acharya et al. teach the Hb-PEG conjugate composition having formula "IV" wherein the PEG moiety is represented by "$-[O-CH_2-CH_2-]_n$" (see also col. 3, lines 63-67, and "*Discussion of art*"); in said formula, "*m*" is an integer "2 to about 16" (see col. 7, line 27) and "Z" is "Hb" conjugated (se col. 7, line 31) wherein "*m*" indicates number of PEG conjugated which meets the instant limitation "*Hb modified to have six ± one PEG*" in claim 8.

Acharya et al. teach that, in step (i), the thiolation of "Hb" is carried out under the reaction condition that the thiolating agent is about 5-20 fold molar excess over the concentration of Hb (col. 8, lines 7-10); this meets the limitation of claim 8, step (a).

The above Acharya et al. teachings are applied to claim 8.

"Thiolating agent is about 5-20 fold molar excess over the concentration of Hb" taught by Acharya et al., as applied to claims 9-10 and 13-16.

In Figure 6, and col. 3, lines 23-25, Acharya et al. teach that the "PEG compound", i.e., "Mal-PEG 5000", wherein "Mal" refers to malemimidyl group (see col. 4, lines 1-2), as applied to claims 17-18.

Since the non-hypertensive is an inherent property of the PEGylated Hb (see the discussion set forth at page 4, 7th paragraph, the Office action mailed 7/27/07), the above Acharya et al. teachings are applied to claims 19-21.

At col. 53 line 53 to col. 6, line 3, Acharya et al. teach that PEGlation of the thiolated Hb is performed under the reaction condition that the thiolated "Hb" concentration is 0.1 mM-3.0 mM, and, the concentration of the "PEG compound" (having formula of "Ic", see col. 5, line 48), i.e., the maleimidized PEG, is about 0.2 mM- 6.0 mM (NOT that *0.2 M* which is considered to be typo error since Acharya et al. teach a two-fold molar excess of maleimized PEG).

Acharya et al. teaches reacting the thiolated Hb with a 2-fold molar excess of maleimide-PEG and does not expressly teach reacting the thiolated Hb with 16-30 fold excess of PEG.

Nho et al. teach that "PEG-modified hemoglobin compounds…exhibit superior oxygen transport capabilities, extended half-life, and importantly, low immunogenicity" (col. 7, lines 57-60). Nho et al. teaches, "According to a specific embodiment of the invention, between about 10 and 20 percent of bHb surface lysines are PEG-modified in order to result in substantial intravascular retention time. This corresponds to approximately between five and ten PEG molecules conjugated to one molecule of hemoglobin" (col. 15, lines 43-48) and further teaches, "The amount of PEG modification may be controlled by altering the ratio of PEG to hemoglobin in the reaction mixture" (col. 15, lines 41-43).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Acharya and Nho to use an 16-30-, 18-22- or 20-fold molar excess of PEG in the method of Acharya in order to achieve an Hb-PEGylated molecule. One would have been motivated to do this because of the teaching of Nho et al. to have between five and ten PEG molecules conjugated to Hb and further in view of the teaching of Nho et al. that the number of PEGs can be controlled by "altering the ratio of PEG to hemoglobin in the reaction mixture". It would have been routine experimentation for one of ordinary skill in the art to vary the concentration of PEG to arrive at a workable or optimal concentration for optimizing the oxygen transport capabilities, half-life, and immunogenicity (Nho et al.) or oxygen affinity of the modified Hb as taught by Acharya et al. (see col. 1, last line to col. 2, lines 1-4), and/or increasing the hydrodynamic volume of Hb through conjugating chains (polymers) to said Hb protein (see col. 5, lines 9-11), particularly as Nho et al. acknowledges that the number of PEGs on a molecule of Hb is a direct result of the ratio of PEG to Hb. It would have been obvious to the ordinarily skilled artisan such as biochemist to optimize and determine/choose desired concentrations for a person of ordinary skill also is a person of ordinary creativity, not an automaton, and thereby, arrive at instant concentration range with expectation of success in developing the method of making the PEG modified Hb proteins.

Applicant appears to take the position that invention is not obvious from the '943 patent because "the claimed process would produce a PEGylated Hb having the claimed six + one PEG chains, where in addition the PEGylated Hb produced by the claimed method has advantageous, non-hypertensive properties" (instant remarks at p. 7). Applicant's argument appears to suggest that the claimed invention yields an PEGylated Hb with unexpected properties. However, even

assuming *arguendo* the claimed process yields unexpected results, the claimed invention is not commensurate in scope with the evidence provided by the specification at, *e.g.,* pp. 21-22, which discloses $(PEG_{5K})_6$-HbA as having antihypertensive activity.

New- Provisional Rejection -Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 8-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27 and 29 of co-pending Application No. 11921064 ('**064**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 27 and 29 of '064 disclose a method of producing PEG conjugated Hb comprising reacting Hb with a thiolating agent, followed by reacting the thiolated Hb with PEGylating agent,

e.g., maleimide PEG (claim 29). This method is an obvious variation of instant method of claims 8-16. This is because the '064 application discloses (sentence bridging pp. 10-11), "the hexaPEGylated Hb [(SP-PEG-5K)6-Hb] generated by PEGylation of Hb at a concentration of 0.5 mM in the presence of 5 mM iminothiolane and 10 mM maleimide phenyl PEG". The specification of '064 sets forth that PEG chain has molecular weight of 200-20,000 daltons (see paragraph [36-37]). This method falls within the scope of claims 27 and 29 of the '064 application and supports an embodiment that would fall within the scope of claims 8-21 of this application.

Since "not produce hypertension in a subject" is an inherent property of the claimed Hb-PEG conjugate, instant claims 19-21 are included in the provisional rejection.

Conclusion

No claims are allowed.

Discussion of the art

The art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

● Wikipedia (2008, updated) Polyethylene glycol, "en.wikipedia.org/wiki/ Polyethylene_glycol", pages 1-4) teaches that PEG polymer has "unit" structure "HO-(CH_2-CH_2-O-)$_n$-H".

●Discussions of references related to obviousness type double patenting

Claims 17-21 of 11919788 disclose a method of producing PEG conjugated Hb comprising conjugating directly – without the use of a thiolating compound – a maleimide-modified PEG to thiol moiety of cysteine residues of Hb protein. This method differs from

instant method of claim 8 in that the claim 8 method requires first reacting Hb with 8-15 excess of thiolating agent. Thus, 11919788 is not an obviousness double patenting reference over the current invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

/Samuel W Liu, Ph.D./
Examiner, Art Unit 1656
June 25, 2008

/David J. Steadman/
Primary Examiner, Art Unit 1656